Attorney's Docket No. 35718/237005 (5718-118) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Abad *et al.*	Confirmation No.:	5409
Appl. No.:	10/032,717	Group Art Unit:	1638
Filed:	October 23, 2001	Examiner:	A.R. Kubelik
For:	GENES ENCODING NOVEL BACILLUS THURINGIENSIS PROTEINS WITH PESTICIDAL ACTIVITY AGAINST COLEOPTERANS		

Commissioner for Patents
P.O. Box 1450
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APPEAL BRIEF UNDER 37 CFR § 1.192 SUBMITTED IN RESPONSE TO NOTIFICATION OF NON-COMPLIANCE

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed March 1, 2004, the Notification of Non-Compliance mailed June 28, 2004, and the Amendment After Final submitted herewith. Applicants believe that the issues identified in the Notification of Non-Compliance have all been addressed in this revised Appeal Brief and by the Amendment After Final submitted herewith. Applicants respectfully request that this Appeal Brief and the Amendment be entered in the case.

1. ***Real Party in Interest.***

The real party in interest in this appeal is E.I. du Pont de Nemours and Company, the assignee of the above-referenced patent application.

2. ***Related Appeals and Interferences.***

There are no related appeals and/or interferences involving this application or its subject matter.

3. ***Status of Claims.***

Claims 1-3, 9-12, 17-19, 38-40, 43-46, 49-52, and 55-64 are the subject of this appeal. Claims 4-8, 13-16, 20-27, 41, 42, 47, 48, 53, and 54 have been cancelled.

4. ***Status of Amendments.***

An Amendment After Final was filed on February 2, 2004, to make changes to the claims pursuant to suggestions by the Examiner and to place the claims in better condition for further prosecution. An Advisory Action was mailed February 18, 2004, indicating that the proposed amendments would not be entered. Applicants filed a Notice of Appeal, and the Examiner issued a Notice of Non-Compliance dated June 28, 2004. Applicants are filing herewith a second Amendment After Final to cancel claims 42, 48, and 54, which were the claims in the case that included hybridization limitations. With the entry of this second Amendment After Final, the number of issues on appeal will be reduced to two issues as set forth below.

5. ***Summary of the Invention.***

The pending claims of the present invention are drawn to an isolated nucleic acid comprising a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO:1, wherein said nucleotide sequence encodes a polypeptide which is pesticidal for at least one pest belonging to the order Coleoptera (see, *e.g.*, page 11, line 18; page 12, line 10; page 18, line 29; and page 3, line 20). The claims of the present invention are also drawn to a transformed plant comprising in its genome at least one stably incorporated nucleotide construct comprising a nucleotide sequence encoding a polypeptide operably linked to a promoter that drives expression of said polypeptide, wherein said polypeptide is pesticidal for at least one pest belonging to the order Coleoptera and wherein said nucleotide sequence has at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO:1 (see, *e.g.*, page and line numbers cited above as well as page 7, line 5). The claims of the present invention are also drawn to a method for impacting an insect pest comprising introducing into a plant or cell thereof at least one nucleotide construct comprising a nucleotide sequence encoding a polypeptide operably linked to a promoter that drives expression of said polypeptide in plant cells, wherein said polypeptide is pesticidal for at least one pest belonging to the order Coleoptera and wherein said nucleotide sequence has at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO:1, whereby an insect pest feeding on said plant or cell thereof is impacted (see, *e.g.*, page and line numbers cited above as well as page 7, line 6).

6. ***Issues.***

Issue 1—Whether claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

Issue 2—Whether claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

7. ***Grouping of Claims.***

Applicants believe that the claims do not stand or fall together. The rejected claims are all "sequence identity claims" which contain limitations that require the nucleotide sequence of the claims to share a specified percent of sequence identity to SEQ ID NO:1. However, some of the sequence identity claims differ from each other in the minimum percent sequence identity that is required and may therefore be found to differ in meeting the requirements of patentability. That is, claims 1, 9, and 17 require that the nucleotide sequence has at least 90% sequence identity to SEQ ID NO:1, while claims 55, 58, and 63 contain limitations requiring the nucleotide sequence to have at least 93% identity to SEQ ID NO:1. Claims 56, 59, and 64 contain limitations requiring the nucleotide sequence to have at least 94% identity to SEQ ID NO:1, and claims 38, 43, and 49 contain limitations requiring the nucleotide sequence to have at least 95% identity to SEQ ID NO:1. While Applicants believe that all these claims are allowable, it is conceivable that among claims with differing requirements for percent sequence identity, some claims could be found to meet the enablement and written description requirements while others might not. Therefore, the sequence identity claims do not necessarily all stand or fall together. For example, claims requiring at least 90% sequence identity may stand or fall separately from those claims requiring at least 93% sequence identity.

8. ***Argument.***

(a) Issue 1—Whether claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

In the final Office Action (12/03/03, page 2, #3), the Examiner maintained the rejection of claims 1-3, 9-12, 17-19, 38, 42, 43, 46, 48, 49, 52, and 54 and rejected claims 55-64 under 35 U.S.C. §112, first paragraph, because:

> the specification, while being enabling for nucleic acids encoding SEQ ID NO:2 and 10, expression cassettes comprising the nucleic acid, plants and seeds comprising a construct comprising the nucleic acid and a method of using it to impact a plant pest, does not reasonably provide enablement for any nucleic acid that has 90% identity to SEQ ID NO:1, that hybridizes to SEQ ID NO:1 or that is antisense to a nucleic acid with 90% identity to SEQ ID NO:1....

Claims 42, 48, and 54 have been cancelled in an Amendment After Final filed herewith. Accordingly, this rejection will be discussed with regard to the remaining sequence identity claims.

The enablement rejection encompassed claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64. These claims contain limitations that require the nucleotide sequence of the claims to share a specified percent of sequence identity to SEQ ID NO:1 and thus are referred to herein as the "sequence identity claims." The enablement rejection in the final Office Action only referred to the claim limitation that requires nucleotide sequences to have at least 90% sequence identity to SEQ ID NO:1, but the Advisory Action clarified that the enablement rejection also applied to claims specifying at least 93%, 94%, and 95% sequence identity (*i.e.*, claims 55, 58, and 63 (93%), claims 56, 59, and 64 (94%), and claims 38, 43, and 49 (95%)). Applicants respectfully traverse this rejection and submit that the Examiner is applying an extraordinarily high standard of enablement to the present claims, a standard that is not properly based on case law or on the statute.

Support is provided for the limitations of the claims

First, guidance is provided as to what sequence alterations may be made and still provide a pesticidal polypeptide encompassed by the claim. As discussed further below, endotoxin genes are well known in the art. Applicants have provided the exemplary nucleotide sequence of SEQ ID NO:1 and the exemplary amino acid sequence of SEQ ID NO:2. Indeed, as quoted above, the Final Office Action stated that the specification was enabling for nucleic acids encoding SEQ ID NO:2, and the Examiner indicated that claims drawn to the exemplary disclosed sequences (*i.e.*, claims 39, 40, 44, and 45) would be allowable if rewritten in independent form. The claimed sequences of the invention vary from the exemplary disclosed sequences by structural parameters (*i.e.*, percent sequence identity to SEQ ID NO:1; encoding the amino acid sequence set forth in SEQ ID NO:2). Guidance for determining percent identity of sequences is provided in the

specification on pages 33 through 38. Moreover, the independent sequence identity claims (*i.e.*, claims 1, 9, and 17) specify that the nucleotide sequence encodes a polypeptide which is pesticidal for at least one pest belonging to the order Coleoptera; therefore, these claims (and the claims dependent on them) encompass functional variants. Guidance regarding alterations that allow the sequence to retain the specified pesticidal activity is also provided (see, *e.g.*, p. 18 (providing guidance regarding conservative substitutions of amino acids) and pp. 19-20 (discussing the activity of variants)). Methods for assaying the pesticidal activity of proteins are routine in the art and are also described in the specification, for example, on pages 8 and 29 and in the experimental section in working examples such as Example 4 (pp. 65-66), Example 6 (p. 67), and Example 7 (p. 69). These working examples teach methods for assaying pesticidal activity of proteins and demonstrate results obtained using these assays. In this manner, Applicants have provided guidance regarding what changes may be made to allow the endotoxin sequence to retain the specified pesticidal activity.

B. thuringiensis δ-endotoxins are well-known in the art, and further support and guidance is provided by working examples

The Examiner concludes that "[t]he specification provides no guidance as to which amino acids of SEQ ID NO:2 are critical for function." Applicants respectfully disagree with this conclusion. As noted above, Applicants have provided the exemplary nucleotide sequence of SEQ ID NO:1 and the exemplary amino acid sequence of SEQ ID NO:2. The claimed sequences of the invention vary from this sequence by structural parameters (*i.e.*, percent sequence identity to SEQ ID NO:1). As discussed extensively in the specification (*e.g.*, pp. 3, 7, 11-12, 15, 24-25), the disclosed exemplary sequence of SEQ ID NO:2 is a *Bacillus thuringiensis* Cry-8-like δ-endotoxin. The *B. thuringiensis* δ-endotoxins are an extremely well-characterized group of proteins. As discussed in the specification at pp. 24-25:

> Many of the δ-endotoxins are related to various degrees by similarities in their amino acid sequences and tertiary structure, and means for obtaining the crystal structures of *B. thuringiensis* endotoxins are well known. Exemplary high-resolution crystal structure solution of both the Cry3A and Cry3B polypeptides are available in the literature. The inventors of the present invention used the **solved structure of the *Cry3A* gene** (Li *et al.* (1991) *Nature* 353:815-821) to produce a homology model of the Cry8

> δ-endotoxin disclosed and claimed herein as SEQ ID NO:2 to gain insight into the relationship between structure and function of the endotoxin, and to design the recombinantly engineered proteins disclosed and claimed herein. A combined consideration of the **published structural analyses** of *B. thuringiensis* endotoxins and the reported function associated with particular structures, motifs, and the like indicates that specific regions of the endotoxin are correlated with particular functions and discrete steps of the mode of action of the protein. For example, **δ-endotoxins isolated from *B. thuringiensis* are generally described as comprising three domains, a seven-helix bundle that is involved in pore formation, a three-sheet domain that has been implicated in receptor binding, and a beta-sandwich motif** (Li *et al.* (1991) *Nature*, 305: 815-821).

As discussed in more detail in the specification (see, *e.g.*, p. 25), the inventors made use of this knowledge in the art to design specific mutations in the Cry8-like proteins to enhance their pesticidal activity. This strategy was successful in creating altered endotoxins with increased toxicity, as demonstrated by the data presented in working Example 6. Thus, as demonstrated by working examples in the specification, those of skill in the art (*i.e.*, the inventors) were able, in view of the extensive knowledge in the art about *B. thuringiensis* δ-endotoxin structure and function, to modify the exemplary wildtype sequences disclosed herein to provide variant endotoxins with enhanced pesticidal activity. In this manner, the data provided in the specification (*e.g.*, Example 6) demonstrate that one of skill in the art would know what amino acids could be changed to provide a protein with pesticidal activity. Accordingly, Applicants submit that adequate guidance is provided as to which amino acids of SEQ ID NO:2 are critical for function.

The data and working examples provided in the specification also demonstrate the enablement of the claimed invention by showing that sequences of the invention that share a relatively low percent identity to the exemplary sequence of SEQ ID NO:1 encode polypeptides that have pesticidal activity against several Coleopteran pests. In Example 4 (specification pp. 65-66), both the full-length endotoxin encoded by SEQ ID NO:1 and a truncated protein encoded by SEQ ID NO:15 were assayed for pesticidal activity against southern corn rootworm. The nucleotide sequence of SEQ ID NO:15 is a truncation of SEQ ID NO:1 which shares about 55% sequence identity with SEQ ID NO:1. In Example 6 (specification pp. 67-69), several truncated proteins were assayed and shown to have pesticidal activity against Colorado potato beetle (see

Table 1, p. 68). These truncated proteins included those encoded by SEQ ID NO:15 and SEQ ID NO:19, which share about 55% and 51% identity, respectively, to the exemplary nucleic acid sequence set forth in SEQ ID NO:1 (alignments performed using BLAST with default parameters). As briefly discussed above, Example 6 also provides assay data for a mutated sequence, NGSR1218-1. This NGSR1218-1 mutant includes the amino acid sequence "NGSR" inserted between amino acids 164 and 165 of the truncated endotoxin of SEQ ID NO:16. The nucleotide sequence encoding this mutant (SEQ ID NO:11) shares about 56% sequence identity with the exemplary nucleotide sequence of SEQ ID NO:1, yet as documented by the data provided in Example 6, both proteins have pesticidal activity. In addition to this data, the specification also provides an exemplary maize-optimized sequence (SEQ ID NO:9) which encodes the same pesticidal polypeptide as SEQ ID NO:15 but shares less than 69% sequence identity with it. Thus, the specification is replete with working examples of sequences that share a relatively low percentage of identity with SEQ ID NO:1 and which encode polypeptides having pesticidal activity. In fact, the percentage of sequence identity shared by the exemplary SEQ ID NO:1 and these sequences in the working examples is much lower than the "at least 90%" of the broadest sequence identity claims.

The Examiner dismisses the working examples provided by Applicants, concluding that the specification teaches only "a fragment," "a single insertion of 4 amino acids in the 669 amino acid long SEQ ID NO:16," and "nucleic acids encoding SEQ ID NO:2" and stating that the specification "is not enabled for nucleic acids that have 90% identity to SEQ ID NO:1 but that do not encode SEQ ID NO:2." Applicants respectfully disagree with this conclusion. Applicants have provided percent identity variants that include both fragments and amino acid changes to the exemplary wildtype sequences of SEQ ID NO:1 and the encoded SEQ ID NO:2 and thus have taught representative species of the genus of sequences having a particular structural relationship to the exemplary wildtype sequences.

The amount of experimentation required to make and use the subject matter of the claims is not undue

The Examiner concludes that "undue trial and error experimentation would be required to make the claimed nucleic acids" (Advisory Action, 2/18/04, continuation sheet). The Federal

Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue, and that a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance as to how the experimentation should proceed. *Id. In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir 1988). In the instant case, the quantity of experimentation required to practice independent claim 1 amounts to two steps: (1) generating a nucleic acid comprising a nucleotide sequence that has at least 90% sequence identity to SEQ ID NO:1; and (2) assaying the encoded polypeptide for functional activity. Such assays, while known in the art, have further been presented in the specification. One of skill in the art would appreciate that both of these steps are within the skill of those in the art and that this degree of experimentation is not considered undue.

Similarly, the amount of experimentation needed to practice the other sequence identity claims is not undue. For example, independent claim 9 recites a transformed plant comprising a nucleotide construct that has a nucleotide sequence with at least 90% sequence identity to the nucleotide sequence set forth in SEQ ID NO:1 and that encodes a polypeptide that is pesticidal for at least one pest belonging to the order Coleoptera. Thus, in addition to the steps required to practice independent claim 1, independent claim 9 requires the transformation of a plant. Plant transformation is routine in the art; thus, the amount of experimentation required to practice claim 9 is not undue. Similarly, in addition to the steps required to practice independent claim 1, the method of independent claim 17 requires that a nucleotide construct be created in which the nucleotide sequence is operably linked to a promoter; that the construct be introduced into a plant or cell thereof; and that an insect pest feeding on said plant or cell is impacted. The performance and/or evaluation required by each of these additional steps is within the skill of those in the art and would not be considered undue experimentation by those in the art. Likewise, the remaining sequence identity claims, which are all dependent on or incorporate the limitations of independent claim 1, 9, or 17, contain additional requirements which are equally within the skill of those in the art.

Applicants note that it is now customary in the art to make and assay a number of sequences for a desired function in order to achieve the best results. For example, common techniques involve what is often referred to as "shuffling," as described for example in U.S.

Patent No. 5,837,458, issued November 17, 1998 with inventors Minshull and Stemmer and entitled, "Methods and Compositions for Metabolic and Cellular Engineering." With such techniques, it is common to mutagenize individual sequences or a set of sequences which are then assayed for a desired activity. Such techniques may even make use of a library of sequences which is recursively mutagenized, screened for function using a functional assay, and re-mutagenized in order to find a sequence exhibiting optimal function. Examples of the use of such techniques include: Minshull and Stemmer (1999) *Current Opinion in Chemical Biology* 3:284-290, entitled "Protein Evolution by Molecular Breeding"; and Christians *et al.* (1999) *Nature Biotechnology* 17: 259-264, entitled "Directed evolution of thymidine kinase for AZT phosphorylation using DNA family shuffling." Such experiments are designed and are intended to encompass the generation and testing of a very large number of variant sequences for a desired function. As indicated by these and other publications in the art, this level of experimentation is now considered routine in the art and thus would not be considered "undue experimentation" under *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir 1988) and *In re Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Int. 1982) (holding that a considerable amount of experimentation is permitted to practice the invention and is not undue if it is merely routine in the art or if the specification provides a reasonable amount of guidance and direction to perform such experimentation).

One of skill in the art could make and use the claimed invention without undue experimentation

It is true that some embodiments of the nucleotide sequence which meet the percent identity limitation of the claims may not encode a polypeptide that has the specified pesticidal activity. However, one of skill would readily be able to use the assays taught in the specification to determine which nucleotide sequences that met the sequence identity limitations of the claims also encoded polypeptides having the specified pesticidal activity. Applicants note that the presence of inoperative embodiments within the scope of the claims does not render the claims invalid. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). Nor would the amount of experimentation required to test a particular polypeptide for pesticidal activity be considered undue by one of skill in the art, as evidenced by

the assay results presented in the specification, for example, in working Examples 4 (pp. 65-66), 6 (p. 67), and 7 (p. 69). The references cited by the Examiner—Lazar *et al.* (1988) *Mol. Cell. Biol.* 8: 1247-52 and Hill *et al.* (1998) *Biochem. Biophys. Res. Comm.* 244: 573-577—illustrate that one of skill would readily be able to determine whether a particular sequence change affected the function of a protein. Accordingly, one of skill in the art would be able to determine the functionality of polypeptides encompassed by the claimed invention without undue experimentation.

The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir 1988). Furthermore, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *Id.* Applicants stress that when evaluating the quantity of experimentation required, the court looks to the amount of experimentation required to practice a single embodiment of the invention rather than the amount required to practice every embodiment of the invention as the Examiner implies. For example, in *Wands*, the claims at issue were drawn to immunoassay methods using any monoclonal antibody having a binding affinity for HbsAg of at least 10^{-9} M. The PTO had taken the position that the claim was not enabled because it would take undue experimentation to make the monoclonal antibodies required for the assay. The Federal Circuit reversed and held that the claims were enabled, as the amount of experimentation required to isolate monoclonal antibodies and screen for those having the correct affinity was not undue. *See Id.* Clearly, the Federal Circuit did not contemplate that every antibody useful in the methods of the claim must be identified. Rather, the court considered the amount of experimentation required to identify one or a few monoclonal antibodies having the required affinity. *See also, Johns Hopkins University v. Cellpro*, 931 F. Supp. 303, 324 (D. Del. 1996), *aff'd in part, vacated in part, and remanded*, 47 USPQ2d 1705 (Fed. Cir. 1998) (stating that "[t]he specification need only enable one mode of making the claimed invention.").

Thus, for the reasons discussed above, Applicants respectfully submit that the sequence identity claims meet the enablement requirement of 35 U.S.C. §112, first paragraph. Based on the knowledge in the art and the guidance provided in the specification, the skilled artisan could

choose among possible sequence modifications to produce polypeptides within the sequence identity parameters set forth in the claims and then test these sequence variants to determine if they retained pesticidal activity. The amount of experimentation needed to perform such an evaluation would not be considered by those of skill in the art to be undue; therefore, the amount of guidance presented in the specification is sufficient to enable the claims. Accordingly, Applicants respectfully submit that the Examiner's rejection of the sequence identity claims 1-3, 9-12, 17-19, 38-40, 43-46, 49-52, and 55-64 under 35 U.S.C. §112, first paragraph, for lack of enablement should be reversed.

(b) Issue 2—Whether claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

In the final Office Action (12/03/03, page 4, #4), the Examiner maintained the rejection of claims 1-3, 9-12, 17-19, 38, 42, 43, 46, 48, 49, 52, and 54 and rejected claims 55-64 under 35 U.S.C. §112, first paragraph:

> [A]s containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reasons of record.... Applicant's arguments...have been fully considered but they are not persuasive."

Claims 42, 48, and 54 have been cancelled in an Amendment After Final filed herewith. Accordingly, this rejection will be discussed with regard to the remaining sequence identity claims.

The written description rejection in the final Office Action encompassed claims 1-3, 9-12, 17-19, 38, 43, 46, 49, 52, and 55-64. These claims contain limitations that require the nucleotide sequence of the claims to share a specified percent of sequence identity to SEQ ID NO:1 and thus are referred to herein as the "sequence identity claims." In maintaining this rejection, the Examiner disregards not only Applicants' arguments but also the case law cited in those arguments. Applicants respectfully submit that the Examiner is applying an extraordinarily high standard of written description to the present claims, a standard that is not properly based on case law or on the statute.

As an initial matter, Applicants note that the written description rejection in the final Office Action only referred to the claim limitation that requires nucleotide sequences to have at least 90% sequence identity to SEQ ID NO:1, but some of the claims included in the rejection specify at least 93%, 94%, and 95% sequence identity (*i.e.*, claims 55, 58, and 63 (93%), claims 56, 59, and 64 (94%), and claims 38, 43, and 49 (95%)). Presumably these claim limitations have also been considered by the Examiner and the basis for rejection would be the same as stated for the 90% sequence identity claims, *mutatis mutandis*.

Also, Applicants note that in the final Office Action (12/03/03, page 4, #4, 3d paragraph), the Examiner stated that "nucleic acids that have 90% identity to SEQ ID NO:1 ***are predictable***, nucleic acids that have 90% identity to SEQ ID NO:1 AND that encode pesticidal proteins are not" (emphasis added). Thus, the written description rejection is on the grounds that there is inadequate description of sequences that both meet the sequence identity requirement of the claims and also meet the functional requirement (*i.e.*, that the encoded polypeptide has pesticidal activity).

The claims meet the written description requirement as articulated by the Federal Circuit

Applicants respectfully submit that the present claims and specification meet the written description requirement of 35 U.S.C. §112, first paragraph, as clarified by *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991); *cert. denied* 112 S.Ct. 169 (1991). Applicants have provided exemplary sequences of the invention as set forth in SEQ ID NO:1. Indeed, in the Final Office Action, the Examiner indicated that claims drawn to the exemplary disclosed sequences (*i.e.*, claims 39, 40, 44, and 45) would be allowable if rewritten in independent form. The claimed nucleic acids are defined in relation to the exemplary disclosed nucleotide sequence of SEQ ID NO:1; that is, the claimed nucleic acids comprise nucleotide sequences that share a specified percentage of sequence identity with SEQ ID NO:1. Applicants have thus provided a structural definition of the sequences of the invention. Applicants have also provided assays by which those of skill in the art can readily assess whether a nucleic acid molecule meeting the nucleotide sequence element of the claims also meets the functional limitation element of the claims. This is what *Eli Lilly*

requires, and Applicants have also conceived the sequences of the invention as articulated in *Amgen*; that is, Applicants are able "to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it." *Amgen*, 18 USPQ2d at 1021.

Applicants further note that the Federal Circuit has explicitly stated that:

> *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003). *See also, Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320, 66 USPQ2d 1429, 1438 (noting that "[i]n more recent cases, however, this court has distinguished *Lilly*" and further noting that in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002), "neither the specification nor the deposited biological material recited the precise 'structure, formula, chemical name, or physical properties' required by *Lilly*.")

B. thuringiensis δ-endotoxins are well-known in the art, and further support is provided in the specification with working examples

As discussed extensively in the specification (*e.g.*, on pp. 3, 7, 11-12, 15, 24-25), the disclosed exemplary sequence of SEQ ID NO:2 is a *Bacillus thuringiensis* Cry-8-like δ-endotoxin. The *B. thuringiensis* δ-endotoxins are an extremely well-characterized group of proteins. As discussed in the specification at pp. 24-25:

> The inventors of the present invention used the **solved structure of the *Cry3A* gene** (Li *et al.* (1991) *Nature* 353:815-821) to produce a homology model of the Cry8 δ-endotoxin disclosed and claimed herein as SEQ ID NO:2 to gain insight into the relationship between structure and function of the endotoxin, and to design the recombinantly engineered proteins disclosed and claimed herein. A combined consideration of the **published structural analyses** of *B. thuringiensis* endotoxins and the reported function associated with particular structures, motifs, and the like indicates that specific regions of the endotoxin are correlated with particular functions and discrete steps of the mode of action of the protein. For example, **δ-endotoxins isolated from *B. thuringiensis* are generally described as comprising three domains, a seven-helix bundle that is**

involved in pore formation, a three-sheet domain that has been implicated in receptor binding, and a beta-sandwich motif (Li *et al.* (1991) *Nature*, 305: 815-821).

As discussed in more detail in the specification on p. 25, the inventors made use of this knowledge to design specific mutations in the Cry8-like proteins to enhance their pesticidal activity. This strategy was successful in creating altered endotoxins with increased toxicity, as demonstrated by the data presented in working Example 6. Thus, the inventors were able, in view of the extensive knowledge in the art about *B. thuringiensis* δ-endotoxins, to modify the exemplary wildtype sequences disclosed herein to provide an endotoxin with enhanced pesticidal activity. In this manner, the data provided in the specification (*e.g.*, Example 6) demonstrate that one of skill would know what amino acids could be changed to provide a protein with pesticidal activity. Accordingly, Applicants submit that adequate guidance is provided as to which amino acids of SEQ ID NO:2 are critical for function and that therefore, Applicants have envisioned the detailed construction of the gene to distinguish it from other materials, thereby meeting the written description requirement.

Applicants note that in the final Office Action, the Examiner stated that "Applicant has not described even one nucleic acid that ... has 90% identity to SEQ ID NO:1 AND that encodes a pesticidal protein." Applicants respectfully disagree with this conclusion. The specification teaches a number of nucleic acids that share relatively low percent sequence identity with SEQ ID NO:1 but encode proteins having pesticidal activity. In Example 4 (specification pp. 65-66), both the full-length endotoxin encoded by SEQ ID NO:1 and a truncated protein encoded by SEQ ID NO:15 were assayed for pesticidal activity against southern corn rootworm. The nucleotide sequence of SEQ ID NO:15 is a truncation of SEQ ID NO:1 which shares about 55% sequence identity with SEQ ID NO:1. In Example 6 (specification pp. 67-69), several truncated proteins were assayed and shown to have pesticidal activity against Colorado potato beetle (see Table 1, p. 68). These truncated proteins included those encoded by SEQ ID NO:15 and SEQ ID NO:19, which share about 55% and 51% identity, respectively, to the exemplary nucleic acid sequence set forth in SEQ ID NO:1 (alignments performed using BLAST with default parameters). Another mutant assayed for pesticidal activity in Example 6 was NGSR1218-1 (encoded by SEQ ID NO:11). The NGSR1218-1 mutant includes the amino acid sequence

"NGSR" inserted between amino acids 164 and 165 of the truncated endotoxin of SEQ ID NO:16. The nucleotide sequence encoding this mutant (SEQ ID NO:11) shares about 56% sequence identity with the exemplary nucleotide sequence of SEQ ID NO:1, yet both encoded proteins have pesticidal activity. The specification also teaches an exemplary maize-optimized sequence (SEQ ID NO:9), which encodes the same pesticidal polypeptide as SEQ ID NO:15 but shares less than 69% sequence identity with it. Thus, the present specification provides multiple working examples illustrating the production of sequences that encode pesticidal proteins and share a relatively low percentage of sequence identity with SEQ ID NO:1. Multiple working examples are presented, illustrating that Applicants were in possession of the claimed invention at the time of filing.

In light of the above statements, Applicants respectfully assert that the present claims and specification satisfy the statutory written description requirement. Accordingly, Applicants respectfully request that the rejection of the sequence identity claims under 35 U.S.C. §112, first paragraph, be reversed.

CONCLUSION

In view of the arguments presented above, Applicants contend that each of claims 1-3, 9-12, 17-19, 38-40, 43-46, 49-52, and 55-64 is patentable. Therefore, reversal of the rejections under 35 U.S.C. §102(b) and 35 U.S.C. §112, first and second paragraphs, is respectfully solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the US Patent and Trademark Office at facsimile number 703-872-9306 on the date shown below.

Lynda-Jo Pikley — July 27, 2004
Lynda-Jo Pikley — Date

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